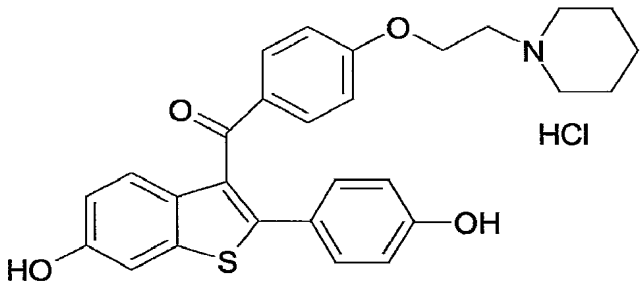
CLAIMS

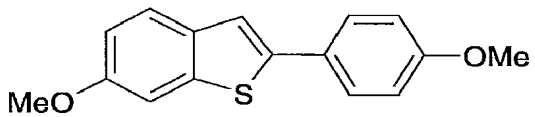
1. Process for preparing raloxifene hydrochloride of formula (I)



(I)

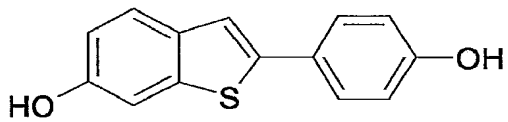
with a purity higher than 98% comprising the following stages:

a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene of formula (II)



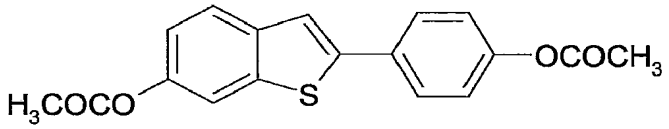
(II)

in pyridine hydrochloride to obtain 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene of formula (III)



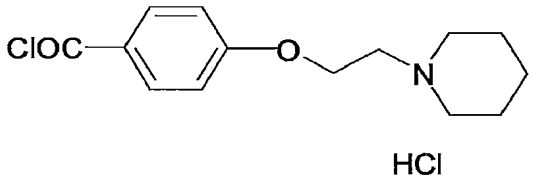
(III)

b) acetylation of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene of formula (IV)



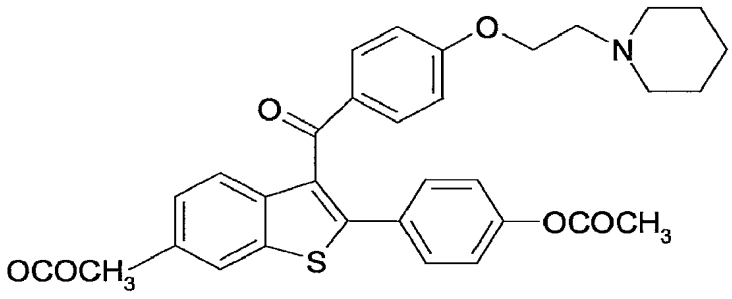
(IV)

c) acylation of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V)



(V)

with aluminium chloride in halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene of formula (VI)



(VI)

d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, according to the following operative modalities:

d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene with alkaline hydroxide in alcohol solvent,

d2) acidification of the product obtained in the preceding stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with the strong acid,

characterised in that the strong acid used in stage (d2) is concentrated hydrochloric acid.

2. Process as claimed in claim 1, characterised in that the pyridine hydrochloride used in stage (a) is prepared in situ by adding concentrated hydrochloric acid to pyridine and distilling off all the water to obtain a thick but stirrable residue.

3. Process as claimed in claim 1 or 2, characterised in that the demethylation reaction or stage (a) of the process of the present invention is also conducted in the presence or tributylamine.

4. Process as claimed in claim 3, characterised in that tributylamine is used preferably in weight ratios with respect to 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) of between 0.5 and 2.

5. Process as claimed in claim 4, characterised in that stage (a) is conducted at a temperature between 170 and 180°C.

6. Process as claimed in any one of claims 1-5, characterised in that acetic anhydride is used as acetylating agent in the presence of triethylamine in ethyl acetate.

7. Process as claimed in any one of claims 1-6, characterised in that the 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V) used in stage (c) is prepared in situ, by reacting 4-(2-piperidinoethoxy)benzoic acid hydrochloride with thionyl chloride in methylene chloride in the presence of pyridine, without isolating the reaction product.

8. Process as claimed in any one of claims 1-7, characterised in that stage (c) is conducted in methylene chloride.

9. Process as claimed in claim 8, characterised in that stage (c) is conducted according to the following operative modalities: 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is added to non-isolated 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V) and prepared in

situ as in claim 7 and the aforesaid mixture is poured onto a mixture consisting of methylene chloride and aluminium trichloride.

10. Process as claimed in any one of claims 1-9, characterised in that the 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is not isolated, but is used in the crude state in the subsequent reaction (d).

11. Process as claimed in any one of claims 1-10, characterised in that stage (d1) is conducted using methanol as alcohol solvent and excess 30% sodium hydroxide.

12. Process as claimed in any one of claims 1-11, characterised in that stage (d2) is conducted directly on the reaction mixture derived from stage (d1) to which are added equal weight quantities of water and ethyl acetate and finally 37% concentrated hydrochloric acid.

13 Process as claimed in claim 1-12, characterised in that the suspension obtained in stage (d2) is washed with equal weight quantities of water and ethyl acetate.

14. Process as claimed in any one of claims 1-13, characterised in that raloxifene hydrochloride has an HPLC purity >98%.

15. Process as claimed in any one of claims 1-14, characterised in that raloxifene hydrochloride derived from stage (d2) is crystallised from an alcoholic solvent.

16. Process as claimed in claim 15, characterised in that said solvent is methanol possibly in the presence of HCl.

17. Process as claimed in any one of claims 15 and 16, characterised in that raloxifene hydrochloride is obtained with a purity greater than 99%.

18. Process as claimed in any one of claims 15 and 16, characterised in that a further crystallisation from raloxifene hydrochloride from alcohol solvent is conducted.

19. Process as claimed in claim 18, characterised in that said crystallisation is conducted in methanol possibly in the presence of HCl.

20. Raloxifene hydrochloride with a purity greater than 99.7%.

21. Raloxifene hydrochloride as claimed in any one of claims 17 – 20, characterised in that it contains aluminium in a quantity less than 5 ppm.

22. Raloxifene hydrochloride as claimed in any one of claims 17-21 characterised in that it contains raloxifene hydrochloride N-oxide in a quantity less than 0.05%.

23. Raloxifene hydrochloride as claimed in claim 22, characterised in that said impurity is contained in a quantity less than 0.01%.

24. Raloxifene hydrochloride as claimed in any one of claims 20-23, characterised by having a D(0.9) ≤100µm and a D(0.5) ≥40µm.

25. Raloxifene hydrochloride as claimed in claim 24, characterised, after a further sieving, by having a D(0.9) between 50 and 65 µm and a D[4.3] ≥20µm.